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Methimazole-induced hypothyroidism paradoxically decreases homocysteine

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Abstract

Clinical hypothyroidism is associated with hyperhomocysteinemia, whereas the opposite is seen in hyperthyroidism. The effects of mild thyroid dysfunction on homocysteine concentrations are not known. We performed the following study to investigate this.

Total homocysteine, vitamins B_6 and B_{12}, folate, fibrinogen, plasminogen activator inhibitor type 1, and lipids were measured in 11 subjects at baseline and after methionine loading. Subjects began methimazole (MMI), 40 mg daily, and were restudied during 2 stages of hypothyroidism. Liothyronine was added and subjects were restudied once thyrotropin normalized. Methimazole was stopped and studies were repeated during 2 stages of hyperthyroidism. Data were analyzed using repeated-measures analysis of variance.

Post-methionine homocysteine decreased in each hypothyroid study compared with baseline (28.8 ± 10.7, 27.5 ± 9.9 vs 34.4 ± 9.2 μmol/L, respectively). In addition, both fasting and post-methionine homocysteine decreased in the euthyroid/MMI study arm compared with baseline despite equivalent thyrotropin values (fasting, 7.5 ± 3.0 vs 8.8 ± 3.5 μmol/L, $P < .05$; and post-methionine, 27.2 ± 10.6 vs 34.4 ± 9.2 μmol/L, $P < .05$, respectively). Fasting homocysteine decreased in the first hyperthyroidism study arm compared with baseline (6.6 ± 2.3 vs 8.8 ± 3.5 μmol/L, $P < .05$) and post-methionine homocysteine decreased in both hyperthyroid arms compared with baseline (25.2 ± 8.1, 24.2 ± 10 vs 34.4 ± 9.2 μmol/L, $P < .05$ respectively).

In conclusion, mild thyroid dysfunction changes homocysteine metabolism. Unexpectedly, our results suggest a homocysteine-lowering effect of MMI.

1. Introduction

Hypothyroidism increases the risk for development of cardiovascular disease, largely because of a worsening cardiovascular risk factor profile including diastolic hypertension, hypertriglyceridemia, hypercholesterolemia, low high-density lipoprotein (HDL) cholesterol, and increased lipoprotein(a) (Lp[a]) [1]. However, these factors do not entirely explain the increased risk of cardiovascular disease seen in hypothyroidism [2]. Recent studies have demonstrated that homocysteine concentrations are higher in patients with hypothyroid compared with euthyroid controls [3-6].

Hyperhomocysteinemia is a risk factor for occlusive cardiovascular disease [7-12]. Evidence for association of hyperhomocysteinemia and cardiovascular disease was first reported in the late 1960s, when autopsy studies demonstrated extensive atherosclerosis and arterial thrombosis in 2 children with hyperhomocysteinemia secondary to genetic mutations [13]. Since then, numerous studies have confirmed the association between homocysteine and cardiovascular disease [7-12,14].

Homocysteine, a sulfated amino acid, is an intermediary product in methionine metabolism [15]. Once formed, it can follow 1 of 2 metabolic fates. In the remethylation pathway, homocysteine is remethylated back to methionine. This reaction is catalyzed by the enzyme, methionine synthetase, and requires both B_{12} as a necessary cofactor and 5-methyltetrahydrofolate, derived from folate, as a methyl donor. Alternatively, homocysteine can be converted to cysteine. This transulfuration pathway is regulated by the enzyme, cystethionine β-synthetase, and requires vitamin B_6 as a cofactor [15,16]. Finally, homocysteine released in

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the circulation and eventually excreted serves as an alternative method of disposal.

The mechanism of thyroid-induced changes in homocysteine metabolism is currently unknown. Possible mechanisms include changes in the activity or concentration of enzymes necessary for metabolism of homocysteine. Alternatively, changes in the concentrations or biologic activity of vitamin B_{12} or B_6, and/or folate may occur in response to altered thyroid homeostasis [16]. Indeed, we have previously reported that vitamin B_{12} biologic activity is altered during hyperthyroidism and may actually cause hyperhomocysteinemia [17]. To date, no studies have evaluated the effects of mild (subclinical) thyroid dysfunction on homocysteine metabolism. In addition, the earlier studies were conducted in subjects with underlying thyroid disorders, including autoimmune thyroid disease or malignancy, disease states that may be associated with altered immune function and/or pro-inflammatory states [3-6]. States of inflammation and/or altered immune function may adversely affect homocysteine metabolism independent of thyroid activity [18,19].

The purpose of this study was twofold: (1) to determine the effects of mild thyroid dysfunction in otherwise healthy subjects on homocysteine concentrations and other metabolic parameters associated with cardiovascular disease, including fasting lipids and Lp(a). In addition, fibrinogen and plasminogen activator inhibitor type 1 (PAI-1) concentrations were measured to determine if mild thyroid disease adversely effected these markers of fibrinolysis/thrombosis; and (2) to determine if any of the cofactors required for homocysteine metabolism are affected by alterations in thyroid homeostasis.

2. Methods

2.1. Participants

The study was approved by the Human Research Review Committee at the University of New Mexico and conducted in the General Clinical Research Center.

Healthy volunteers between the ages of 18 and 40 years were invited to participate. All subjects demonstrated an understanding of the study protocol and signed the approved study informed consent. Subjects were excluded if they had a history of cardiovascular, kidney, or thyroid disease. Subjects were also excluded if they had evidence of vitamin B_{12}, folate, or estrogen deficiencies, or if they were taking vitamin supplements or estrogen.

2.2. Study procedures

Subjects were admitted to the General Clinical Research Center for a baseline study. After a 10-hour overnight fast, blood samples were obtained to measure total homocysteine, thyrotropin (TSH), fibrinogen, PAI-1, Lp(a), lipids, folate, and vitamins B_{12} and B_6. Bioelectrical impedance analysis (BIA) was performed, using the RJL Quantum BIA Analyzer, to evaluate changes in overall body fat during the study. Participants then underwent a methionine load to stimulate homocysteine production, according to a standard protocol [10]. Briefly, 100 mg/kg of L-methionine powder (Spectrum Chemical, Gardena, Calif) was mixed in a noncaloric-, noncaffeinated-, nonnutrient-supplemented beverage and administered orally. Six hours later, blood samples for homocysteine were obtained. Subjects were then discharged.

2.3. Experimental protocol

The study protocol is shown in Fig. 1. Subjects were instructed to take four 10-mg tablets of methimazole (MMI) (Tapazole, Lilly, Indianapolis, Ind), once daily, to create a hypothyroid state. Thyrotropin levels were measured every 2 weeks. Once the TSH rose to 5 to 10 μIU/mL, hypothyroid study 1 was performed. Methimazole was continued and once the TSH rose to 10 to 20 μIU/mL, hypothyroid study 2 was performed. Subjects were instructed to continue MMI and begin liothyronine (Cytomel, Jones Pharma Inc, St Louis, Mo) 25 μg 2 times a day. Thyrotropin was monitored every 2 weeks. Once the TSH returned to the baseline values, the euthyroid/MMI control study was performed. Methimazole was then discontinued and liothyronine was continued to create a hyperthyroid state. Thyrotropin was monitored every 2 weeks until concentrations fell 0.1 to 0.4 μIU/mL when the first hyperthyroid study was performed. Liothyronine was subsequently continued, and TSH was monitored every 2

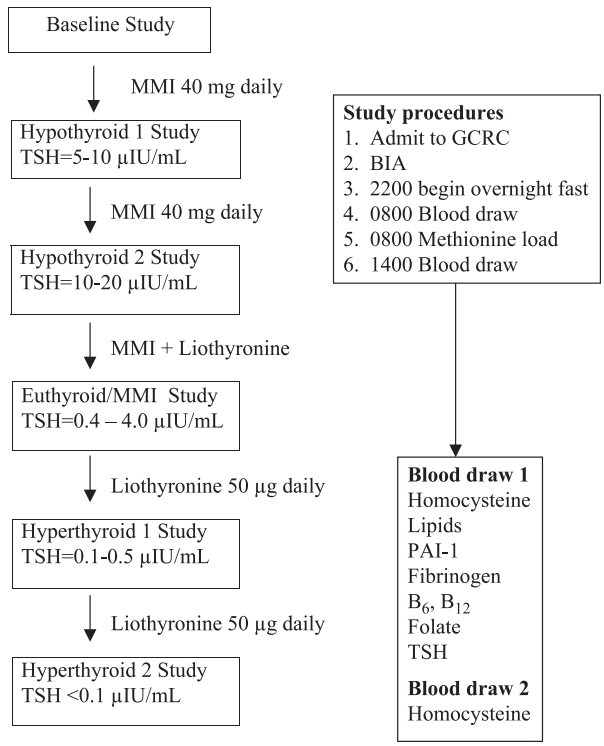

Fig. 1. Study protocol.

weeks until it was suppressed to less than 0.1 μIU/mL when the second hyperthyroid study was performed.

2.4. Biochemical analysis

Pre-iced EDTA tubes were used to collect samples for total plasma homocysteine. Samples were immediately placed on ice, centrifuged for 10 minutes at 2900 rpm at 4°C, and stored at −70°C. DPC Immulite Chemiluminescence was used to determine total homocysteine levels (reference range 5-15 μmol/L, GCRC Core Lab, Albuquerque, NM). Specimens for B_{12}, folate, and TSH were placed in SST tubes and analyzed using DPC Immulite Chemiluminescence analyzer (DPC, Los Angeles, Calif, GCRC Core Laboratory) (TSH [reference range, 0.4-4.5 μIU/mL], B_{12} [reference range, 180-900 pg/mL], and folate [reference range, 3.0-17.0 ng/mL]). Vitamin B_6 was measured by radioenzymatic assay (reference range, 5-30 ng/mL, ARUP Laboratory, Salt Lake City, Utah). Plasminogen activator inhibitor type 1 was measured using a Chromolize PAI-1 kit by biopool, kit catalog number: 1106 (method: a "sandwich-type" enzyme-linked immunosorbent assay; reference range, 2-50 IU/mL; GCRC Laboratories). Fibrinogen was processed in 4.5-mL citrate tubes and measured by a thrombin-based coagulation assay, MLA1800 (reference range, 170-410 mg/dL, Tricore Reference Labs, Albuquerque, NM). Total cholesterol, low-density lipoprotein (LDL), HDL, and triglycerides were measured by spectrophotometry (reference range, 100-200, <100, 35-65, and 130-170 mg/dL, respectively, Tricore Reference Labs). Lipoprotein(a) was measured by immunoprecipitation (reference range, <30.0 mg/dL, Esoteric Inc, Valencia, Calif).

Data were analyzed using SAS/STAT version 8.0 (SAS Institute Inc, Cary, NC). Each subject served as his or her own control. Results of the baseline study were compared with subsequent study arms, using paired Student *t* tests and repeated-measures analysis of variance, using each of the variables measured as dependent variables (baseline homocysteine, post-methionine homocysteine, B vitamins, folate, lipids, fibrinogen, and PAI-1) and the study condition (thyroid state) as the within-subjects factor. Multiple logistic regression analysis was used to determine if any of the variables measured had an independent effect on other variables. Descriptive data were reported as mean ± SE. A probability level of less than .05 was considered significant.

3. Results

3.1. Demographics

Seventeen subjects enrolled in the study. Six (35%) subjects discontinued because of a rash that developed while taking MMI. Three subjects withdrew secondary to side effects that occurred during the study protocol. One subject relocated during the study and was unable to complete the protocol. Eleven subjects thus completed the hypothyroid part of the study (5 females and 6 males) and 7 subjects completed the entire study protocol (3 females and 4 males). The mean age was 29.2 ± 6.3 years. All baseline laboratory parameters were within the reference range. There were no changes in body weight or BIA over the course of the study (data not shown). On average, subjects were hypothyroid for a total of 30 days and it took an average of 130 days of treatment with 40 mg of MMI to reach the first TSH goal (5-10 μIU/mL).

3.2. Cofactors and prothrombotic markers

Results for TSH, fibrinogen, PAI-1, B_{12}, folate, and B_6 under the different study conditions are shown in Table 1. B_6 decreased significantly during the hyperthyroid study conditions compared with baseline. Folate increased during the hyperthyroid studies compared with baseline. There were no significant changes in B_{12}, fibrinogen, or PAI-1 concentrations under any of the study conditions compared with baseline.

3.3. Lipids

Changes in total cholesterol, LDL, HDL, and triglycerides are shown in Table 1. Total cholesterol, LDL cholesterol

Table 1
Results for biochemical tests under each study condition (mean ± SE)

	Baseline (n = 11)	Hypo 1 (n = 11)	Hypo 2 (n = 8)	Euthyroid/MMI (n = 9)	Hyper 1 (n = 7)	Hyper 2 (n = 7)	Reference range
TSH	1.3 ± 0.7	9.1 ± 3.8	21 ± 12	137 ± 0.9	0.26 ± 0.3	0.08 ± 0.09	0.4-4.5 μIU/mL
B_{12}	322 ± 97	364 ± 19	410 ± 20	415 ± 147	360 ± 136	408 ± 167	180-900 pg/mL
B_6	22 ± 7	21 ± 7	22 ± 8	22 ± 13	17 ± 7*	18 ± 7*	5-30 ng/mL
Folate	18 ± 5	18 ± 5	19 ± 7	20 ± 8	20 ± 7.6*	23 ± 8*	3-17 ng/mL
Fibrinogen	258 ± 78	251 ± 76	296 ± 111	294 ± 95	313 ± 128	292 ± 119	170-410 mg/dL
PAI-1	13 ± 4	12 ± 4	15 ± 2	15 ± 5	15 ± 6	ND	2-50 IU/mL
Hcy baseline	8.8 ± 3.5	8.2 ± 2.5	9.7 ± 3.7	7.5 ± 3.0	6.6 ± 2.3	9.7 ± 4.0	5-15 μmol/L
Hcy post-methionine	34.4 ± 9.2	28.8 ± 10.7	27.5 ± 9.9	27.2 ± 10.6	25.2 ± 8.1	24.2 ± 10	μmol/L
Total cholesterol	188 ± 56	205 ± 64	204 ± 77	178 ± 62	180 ± 75	180 ± 73	100-200 mg/dL
LDL	107 ± 32	121 ± 38	117 ± 44	109 ± 38	104 ± 42	105 ± 42	<100 mg/dL
HDL	50 ± 15	51 ± 16	50 ± 19	44 ± 16	49 ± 20	48 ± 20	35-65 mg/dL
Triglyceride	152 ± 46	162 ± 51	187 ± 71	127 ± 45	130 ± 53	131 ± 53	30-170 mg/dL

Hcy indicates homocysteine.
* $P < .05$ vs baseline.

(LDL-C), and triglycerides increased with hypothyroidism but did not reach statistical significance. In addition, there were no differences in Lp(a) between study conditions (data not shown).

3.4. Fasting and post-methionine homocysteine

Total fasting and post-methionine homocysteine concentrations under each study condition are shown in Fig. 2 and Table 1. Post-methionine homocysteine concentrations decreased during each hypothyroid study arm compared with baseline. As TSH increased, homocysteine decreased, suggesting a dose-response curve. However, the differences between hypothyroid study arms were not statistically significant. In addition, there were no differences in fasting values between hypothyroid study conditions and baseline.

During the euthyroid/MMI study, both fasting and postload homocysteine levels were significantly decreased compared with baseline despite equivalent TSH values.

Fasting and post-methionine homocysteine decreased significantly during the first hyperthyroid study compared with baseline. However, during the second hyperthyroid study, only the postload homocysteine was significantly lower than baseline. Similar to the hypothyroid studies, progressive decreases in TSH were associated with progressive decreases in postmethionine homocysteine, but this did not reach significance.

Multiple logistic regression analysis demonstrated that the findings for homocysteine were independent of any of the other variables measured (data not shown).

4. Discussion

In this study, we evaluated the short-term effects of hypo- and hyperthyroidism on both fasting and post-methionine homocysteine. Our findings demonstrate that even short-term, subclinical hyperthyroidism reduces homocysteine. The increase in folate observed during the hyperthyroid study arms could account for the reduction in homocysteine during this phase of the study, but folate increases were offset by decreases in vitamin B_6, a necessary cofactor for the transsulfuration pathway of homocysteine metabolism. Deficiencies of vitamin B_6 have been associated with hyperhomocysteinemia [15]. However, although B_6 levels decreased during the hyperthyroid study, they remained well within the reference range. Finally, the precise role of thyroid hormone homeostasis on homocysteine-dependent cofactors is not clear. For example, we have previously demonstrated that during hyperthyroidism, B_{12} biologic activity may be diminished and cause hyperhomocysteinemia [17]. The effects of alterations in thyroid homeostasis on folate and B vitamins warrant further investigation.

Contrary to previous studies, we were unable to demonstrate increases in homocysteine with hypothyroidism. Indeed, just the opposite occurred. Homocysteine decreased during MMI-induced hypothyroidism in otherwise healthy volunteers. Similarly, the euthyroid/MMI control study was also associated with lower fasting and post-methionine stimulated homocysteine compared with baseline. Although this is an unexpected observation, it has several interesting ramifications. First, more prolonged hypothyroidism may be necessary to develop the necessary

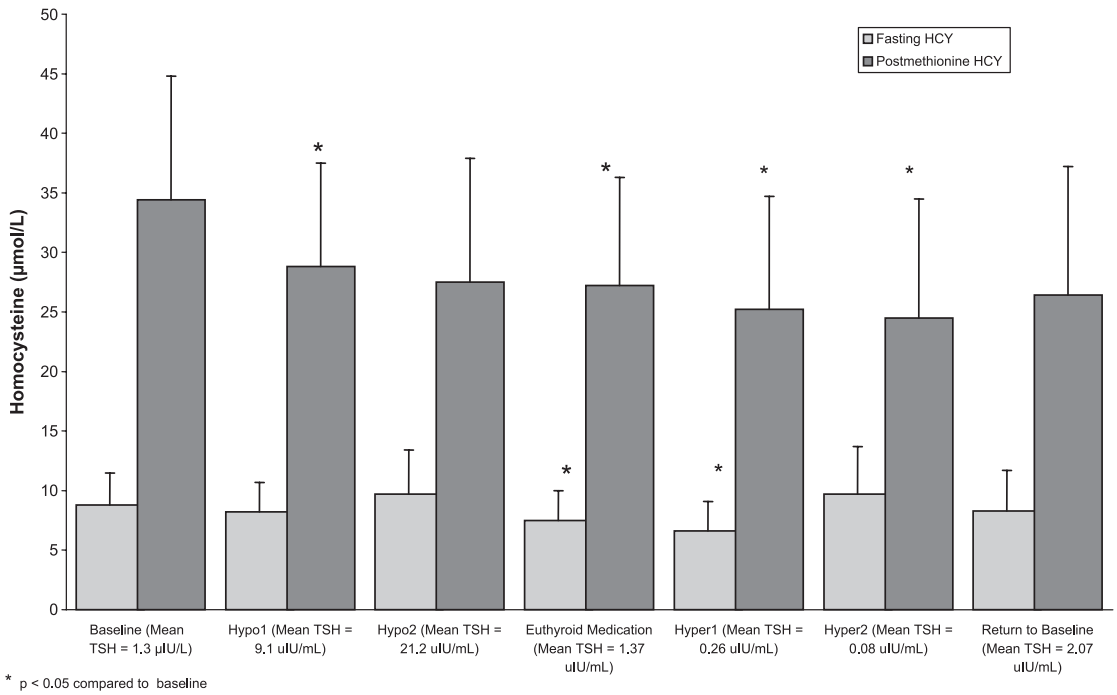

Fig. 2. Changes in fasting and post-methionine homocysteine by study condition.

metabolic milieu for hyperhomocysteinemia to occur. However, Hussein et al [5] demonstrated increases in homocysteine in patients with thyroid cancer who became acutely hypothyroid after thyroidectomy and hormone withdrawal in preparation for radioactive iodine therapy. The duration of hypothyroidism was only 4 to 6 weeks. Similarly, Catargi et al [4] demonstrated hypothyroid-induced hyperhomocysteinemia after only 2 weeks of hypothyroidism. Second, more severe hypothyroidism may be necessary to develop elevations in homocysteine. Compared with our second hypothyroid study (mean TSH = 21.2 μIU/mL), these earlier studies were conducted in patients who were profoundly hypothyroid. Third, as suggested by the euthyroid/MMI control study, MMI itself may alter homocysteine metabolism independent of its effects on thyroid activity. Mechanisms explaining MMI-induced reduction in homocysteine are not clear. Possibilities include MMI-induced increases in the cofactors or enzymes required for homocysteine metabolism. Unfortunately, we were unable to measure enzyme levels directly. However, the lack of significant differences in B_{12}, B_6, and folate during either MMI/hypothyroid study arm or the euthyroid/MMI control arm compared with baseline largely rules out an effect of MMI on homocysteine-dependent cofactors.

Alternatively, MMI may result in changes in hepatic or renal function and could influence homocysteine, and methionine disposal independent of its effect on homocysteine metabolism.

Interestingly, in patients with Graves' disease, treatment with MMI appears to modulate the underlying immune dysfunction associated with this condition, independent of its effects on thyroid homeostasis [20-24]. Homocysteine itself appears to be increased by pro-inflammatory and immune processes [17,18]. Thus, MMI, through its immunomodulating properties, may counteract the effects of hypothyroidism on homocysteine metabolism, resulting in the observed decrease in homocysteine.

Previous studies have that demonstrated that hypothyroidism causes hypercholesterolemia [1]. Our findings suggested a trend toward increasing total cholesterol, LDL-C, and triglycerides during the hypothyroid studies, but these did not reach statistical significance. Similarly, Lp(a), a highly atherogenic variant of LDL-C, did not differ under any study condition. Hypothyroidism has also been associated with elevated fibrinogen concentration, leading to a prothrombotic state further increasing cardiovascular risk [25]. However, neither fibrinogen nor PAI-1 activity levels changed under any of the study conditions. The short duration of the study and mild degree of both hypo- and hyperthyroidism attained probably account for the lack of change in these parameters.

Interestingly, a larger than expected number of study subjects developed an allergic reaction to MMI (35%). This is much higher than rates reported in the literature, approximately 13% [26]. In addition, the time to become hypothyroid was surprisingly long, approximately 130 days. Treatment of hyperthyroidism with MMI is usually effective by 5 to 8 weeks [27,28].

Limitations of our study include the small sample size and the high drop out rate. In addition, the short duration of each of the study conditions and the mild degree of hypo- and hyperthyroidism may have prevented us from finding more significant changes, particularly in lipids and fibrinogen.

In conclusion, the current study demonstrates that during MMI-induced short-term hypothyroidism, not only is there not an increase in homocysteine, just the opposite occurs, homocysteine decreases. We speculate that MMI, through its immunomodulating properties, may prevent hypothyroid-induced hyperhomocysteinemia and indeed may decrease homocysteine concentrations independent of it effects on thyroid homeostasis. Further investigation of the role of MMI as an anti-inflammatory agent is warranted.

Acknowledgments

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